Asian Journal of Applied Science and Technology (AJAST)
Volume 9, Issue 2, Pages 161-169, April-June 2025

Vein viewer: An innovative and emerging NIR-Hb flyover technology in healthcare system

Tirtha Sardar[1], Prayashi Dey[2], Dipsikha Manna[3] & Sarmishtha Chatterjee[4*]

[1,2]*B.Sc Medical Laboratory Technology,* [3]*Faculty, Department of Anatomy and Physiology,* [4]*Assistant Professor, Department of Anatomy and Physiology,* [1,2,3,4]*Belur Sramajibi Swasthya Prakalpa Samity, Bally, Howrah, West Bengal, India. Email: sarmishthaobesity@gmail.com*[*]

DOI: https://doi.org/10.38177/ajast.2025.9215

Article Received: 14 April 2025 *Article Accepted: 19 June 2025* *Article Published: 25 June 2025*

ABSTRACT

Symbiotic relationship in biophysical researches to clinical translations, have tremendously altered the facets of biomedical science and engineering to afford powerful diagnostic and therapeutic competence arraying from basic research to medical and paramedical sectors. Realizing the biophysical research into the fundamental understanding of the spatiotemporal dynamics of receptors on the cell membrane and their functional consequences has enormous potential to improve admitted or home care patient outcome. Based on this fact, vein-finding devices exploit near-infrared (NIR) light (≈ 740nm–760 nm) at a distance of up to several centimetres to distinguish veins properly from arteries and surrounding tissues by the selective absorption of NIR radiation. This supports the access to the vein without the need for several punctures. Vein restraining deoxygenated Hb is potentially bridging with the optical coefficient (absorption and scattering coefficient) of NIR light and proceeds for the prevention of auto-haemolysis and reflection of infrared light simultaneously. This review outlines the basic strategic roadmap for bridging between biophysics and clinical settings in the term of NIR and Hb. Paradigm shift of biophotonics to biomedical sectors consequently reveals innovative technologies for clinical theronostics.

Keywords: Near Infrared Light; Haemoglobin; Biophotonics; Vein-viewer; Biomedical; Absorption; Accu-vein; Autofluresence; Blood-Oxygen-Level-Dependent; Venipuncture.

1. Introduction

"Science be taught as science is practiced", recommended by the American Association for the Advancement of science (AAAS) [1,2,3]. The teaching approach must be consistent with the nature of scientific injury and discovery [4]. On this wise approaches enhance the cognisant and explicit link for new information with previous knowledge [3]. Accordingly, the efficiency based requirement of a physician or laboratory technologist, is needed to identify and inject at proper point in the circulatory system. Hence, vein detector is the primary necessity to obtain intravenous access among admitted patients or home care patients. The everyday invasive medical procedure is venipuncture. Due to time and resource consuming events, excessive venipunctures are significant problem. Difficulty in placing a peripheral intravenous line for child care is very common [4]. Clinical swots have revealed that 51% of children and 83% of toddlers experience immense distress during routine venipunctiure and 36% of young children experienced significant pain [4-6]. Cannula insertion is notoriously complicated in intravenous drug users and patients having repeated courses of chemotherapy [7]. Hereafter, multiple needle pricks raise disquiet, pain and suffering. Most institutions have the guidelines which permit no more than 2-4 intravenous insertion attempts. The incapability to ascertain an intravenous line, moreover impacts negativity on the laboratory technologist and the nursing staff, leading to frustration and deteriorating self-confidence [3,8].

A number of approaches have been developed to improve the visibility and palpability of peripheral veins [5,8,9, 10]. There are four main stratagems [10]: a) manual process with the aids of chemicals [11]. These are not suitable for children and not effective for dark people. b) The use of ultrasound guided procedures [12]. These have the disadvantage of the need for additional trained staff and expensive equipment. c) The use of secondary light sources [13]. It requires a darkened room and can cause burns. d) The visualization of the venous system by means of near

infrared (NIR) [14,15,16,17,18]. It takes a great advantage of the differential absorption to clearly distinguish veins from arteries and surrounding tissues [10,19].

Vein viewers are the vascular admittance devices that demarcate veins (carrying deoxygenated haemoglobin (Hb)) lying in the subcutaneous layer of the skin to identify potential venipuncture sites. Henceforth, highlighting the NIR-Hb interference-technical details of the vein viewer devices are beyond the scope of this review.

1.1. Study Objectives

This review article summarized to address the following key findings:

1) Vein visualization.
2) Factors affecting Hb affinity for oxygen.
3) Selection of wavelength of NIR.
4) Understanding NIR-Hb interference.
5) Assessing the impact of Hb interference on vein visualization.

2. Vein Viewer

French physicist Pierre Aigrain in 1967 is coined the term photonics. It is a branch of science and technology dealing with all methodologies and technologies of light and its interaction with any matter [20,21]. Biophotonics, a multidisciplinary scientific field, merge the light-based technology particularly with biological materials and biomedical applications. Based on this fact of biophotonic imaging of the potential clinical intra-operative tool, Herbert Zeman invented the first vein-finding device in 1995 to image subcutaneous veins [14,22]. Many of these devices exploit near-infrared (NIR) light (≈ 740nm–760 nm) at a distance of up to several centimetres that is obtainable on the skin surface. This NIR light is absorbed by deoxygenated haemoglobin rich blood, while from reflected from the arteries and remaining tissues [10,19,22]. The arrangement progresses with the returned images, adjoins colour and exhibits the image in real time on the skin surface. This supports the vein-visualisation and recognizes bifurcations to enhance the access to the vein without the need for several punctures as well as the possibility of extravasations is thus minimised [14,23]. Vein viewer devices may help to distinguish a healthy vein from a sclerotic vein. The various models of vein viewer devices comprise portable handheld and hand-free devices (with weight ≤500 g), using at the bedside in the hospital, as well as new versions of these devices with improved manoeuvring and configuration options [14]. The most commonly use devices are accu-vein [24], vascu-luminator [25], vein-site [26], vein-viewer vision [27] and vein-viewer flex [28]. The basic phenomena governing the vein viewing devices render selective absorption of NIR radiation to detect only veins. The reason behind this phenomenon is based on the interaction between NIR and haemoglobin (Hb).

2.1. Interaction of NIR and Haemoglobin

Light is an essential physical element, prevailing a wide range of crucial physiological processes in almost all living organisms [29]. Owing to the critical roles of light in our lives, scientists are inspired to explore the interaction between light and organisms. Light has been extensively used both in fundamental research and clinical practice,

regarding cell signal sensing, enzyme activity monitoring, controlled drug release, visual regulation, neuro-modulation, cancer diagnosis and treatment [29,30,31,32]. Light can interact with biological tissues in many different ways. Once entering inside the body, light will usually be reflected, absorbed or scattered by molecules within the tissue. The light wavelength is a key issue concerned in the interaction of light and organisms [29,33,34, 35]. Generally, light with a longer wavelength possesses lower energy. Henceforth, the reaction activity of long wavelength light with most biological tissues is much inferior to short-wavelength light. The visible light (wavelength of 400–700 nm) has been extensively used in biomedical researches and faced high phototoxicity [29, 36,37,38]. In comparison with visible light, NIR light possesses low energy, lower photo-toxicity and higher tissue penetration depth in living systems [29,31,34,35,39]. Consequently, the NIR light-based imaging and photo-regulation strategies have offered a biological transparency window with minimal photo damage and manipulating cell functions with exceptional spatiotemporal precision and sensitivity in deep tissues [29,31,34,40,41]. Due to the minimal scattering and absorption as well as minimal autofluorescence of NIR light by tissues, an *in vivo* deep-tissue imaging with high spatiotemporal resolution can be accomplished by using NIR imaging [31,33].

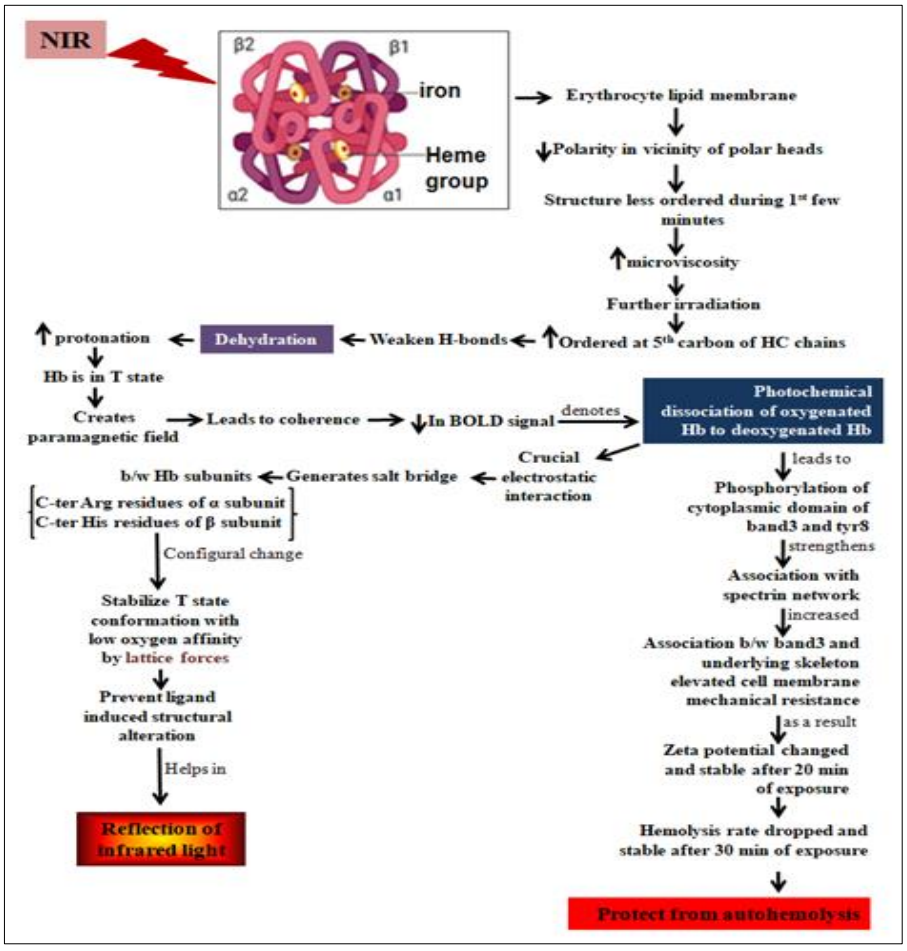

Figure 1. A strategic roadmap between NIR and Hb

Haemoglobin (Hb) is the paradigm of allosteric proteins [42]. It is composed of four subunits ($\alpha_2\beta_2$) and exists in two forms, a taut (T) state and a relaxed (R) state [3]. The T state is the proton-bound deoxygenated form with low affinity for oxygen. In contrast the R state has a high affinity for oxygen. The T and R configurations of Hb direct to diverse electromagnetic absorption and consequently different emission of light [3,42]. However the optical

properties of blood have directed to reasonable results, mostly depend on physiological and biochemical parameters (haematocrit, flow osmolarity, haemolysis and oxygen saturation) [19].

Veins restraining deoxygenated Hb, completely absorb NIR light at the wavelength of approximately 740nm–760nm at a distance upto several centimetres [10]. The reason behind this phenomenon is well demonstrated by a strategic roadmap for bridging between NIR and Hb in the following flow chart (Figure 1). By this way, NIR induces Hb to increase membrane microviscosity and weaken H-bonds [43,44]. This dehydration leads Hb to T state, creating paramagnetic field [45,46,47]. In this fettle, Blood Oxygen Level Dependent (BOLD) signal diminishes to denote photochemical dissociation of oxygenated Hb to deoxygenated Hb [48]. Now from this point a bifurcation leads to phosporylation of cytoplasmic domain of band3 and tyr8 which in turn prevents the autohaemolysis in one way [44] as well as salt-bridge between Hb subunits stabilize T state conformation by lattice forces consequently reflect infrared light in another way [42,49,50].

3. Conclusion

Advancements of light-based optical technologies now-a-days have become one of the most important tools for both fundamental research and clinical practice, impacting on modern medicine, with numerous lasers and optical devices to assess health. In particular, progresses in biomedical optics have enabled gradually more sophisticated technologies. Among them vein detector is aspired to unravel the efficiency based requirement of the medical and paramedical sectors to identify and inject at the proper blood vessels. Development of new, compact and cost-effective vein viewers delivering desired output characteristics will spread out clinical utilities and enlarge treatment outcomes. The versatile role of light in nature hence can sense, monitor and manipulate biological processes. NIR light based strategies have suggested an immense possibility of monitoring and modulating cells like haemoglobin with subcellular and sub-millisecond accuracy in deep tissues, which are inaccessible to other technologies. The insertion of biophysics to clinical translation in medical field thus ensuring the optical diagnostics and imaging may lead to the development of innovative technologies for clinical theronostics and will uncover escalating utilities.

4. Future Suggestions

Optical imagining and diagnosis are now hastily evolving to offer promising solutions for non-invasive disease diagnosis and monitoring in this modern era. The followings are some future suggestions for the advancement in this field.

1) In progression for high resolution imaging, the optical coherence tomography angiography (OCTA) will be crucial for advancing biomedical diagnosis to provide detailed images of blood vessels.

2) Exploration of the application of quantum optics should be perked up for imagining sensitivity and resolution.

3) Integrating multiple optical components onto a single chip for more compact and functional imaging system is hereafter the fundamental requirement.

4) Development of optical sensors for environmental monitoring, biomedical sensing and industrial process control in low resource settings is now in high demand.

Declarations

Source of Funding

The authors received no specific funding for this work.

Competing Interests Statement

The authors declare no competing financial, professional, or personal interests.

Consent for publication

The authors declare that they consented to the publication of this study.

Authors' contributions

All listed authors have contributed sufficiently to the work to be included as co-authors.

Informed Consent

Not applicable.

References

[1] Wood, W.B. (2003). Inquiry-based undergraduate teaching in the life sciences at large research universities: a perspective on the Boyer Commission Report. Cell Biol Educ., 2: 112–116. https://doi.org/10.1187/cbe.03-02-0004.

[2] National Research Council Committee on Undergraduate Biology Education to Prepare Research Scientists for the 21st Century (2010). BIO2010: Transforming Undergraduate Education for Future Research Biologists. Washington, DC: National Academies. https://pubmed.ncbi.nlm.nih.gov/20669482/.

[3] Lujan, H.L., & DiCarlo, S.E. (2022). "Seeing red" reflects hemoglobin's saturation state: a discovery-based activity for understanding the science of pulse oximetry. Adv Physiol Educ., 46(3): 461–467. https://doi.org/10.1152/advan.00093.2022.

[4] Tanner, K.D., Chatman, L., & Allen, D. (2003). Approaches to biology teaching and learning: science teaching and learning across the school-university divide—cultivating conversations through scientist-teacher partnerships. Cell Biol Educ., 2: 195–201. https://doi.org/10.1187/cbe.03-10-0044.

[5] Kuensting, L.L., DeBoer, S., Holleran, R., Shultz, B.L., Steinmann, R.A., & Venella, J. (2009). Difficult venous access in children: taking control. J Emerg Nurs., 35(5): 419–424. https://doi.org/10.1016/j.jen.2009.01.014.

[6] Fradet, C., McGrath, P.J., Kay, J., Adams, S., & Luke, B. (1990). A prospective survey of reactions to blood tests by children and adolescents. Pain, 40(1): 53–60. https://doi.org/10.1016/0304-3959(90)91050-s.

[7] Humphrey, G.B., Boon, C.M., Van Linden van den Heuvell, G.F., & Van de Wiel, H.B. (1992) .The occurrence of high levels of acute behavioral distress in children and adolescents undergoing routine venipunctures. Pediatr., 90: 87–91. https://pubmed.ncbi.nlm.nih.gov/1614786/.

[8] Lenhardt, R., Seybold, T., Kimberger, O., Stoiser, B., & Sessler, D.I. (2002). Local warming and insertion of peripheral venous cannulas: single blinded prospective randomised controlled trial and single blinded randomised crossover trial. BMJ, 325(7361): 409–10. https://doi.org/10.1136/bmj.325.7361.409.

[9] Larsen, P., Eldridge, D., Brinkley, J., Newton, D., Goff, D., Hartzog, T., Saad, N.D., & Perkin, R. (2010). Pediatric peripheral intravenous access: Does nursing experience and competence really make a difference? J Infus Nurs., 33(4): 226–235. https://doi.org/10.1097/nan.0b013e3181e3a0a8.

[10] Juric, S., & Zalik, B. (2014). An innovative approach to near-infrared spectroscopy using a standard mobile device and its clinical application in the real-time visualization of peripheral veins. BMC Med Inform Decis Mak., 14: 100. https://doi.org/10.1186/s12911-014-0100-z.

[11] Sabri, A., Szalas, J., Holmes, K.S., Labib, L., & Mussivand, T. (2013). Failed attempts and improvement strategies in peripheral intravenous catheterization. Biomed Mater Eng., 23: 93–108. https://doi.org/10.3233/bme-120735.

[12] Higgins, D. (2004). Venepuncture. Nurs Times., 100(39): 30–1. https://pubmed.ncbi.nlm.nih.gov/15500234/.

[13] Franco-Sadud, R., Schnobrich, D., Mathews, B.K., Candotti, C., Abdel-Ghani, S., Perez, M.G., Rodgers, S.C., Mader, M.J., Haro, E.K., Dancel, R., Cho, J., Grikis, L., & Lucas, B.P. (2019). SHM Point-of-care Ultrasound Task Force; Soni NJ. Recommendations on the Use of Ultrasound Guidance for Central and Peripheral Vascular Access in Adults: A Position Statement of the Society of Hospital Medicine. J Hosp Med., 14(9): e1–e22. https://doi.org/10.12788/jhm.3287.

[14] Vyas, V., Sharma, A., Goyal, S., & Kothari, N. (2021). Infrared vein visualization devices for ease of intravenous access in children: hope versus hype. Anaesthesiol Intensive Ther., 53(1): 69–78. https://doi.org/10.5114/ait.2021.103515.

[15] Nundy, K.K., & Sanyal, S. (2010). A low cost vein detection system using integrable mobile camera devices. Annual IEEE India Conference INDICON. https://doi.org/10.1109/indcon.2010.5712670.

[16] Francisco, M.D., Chen, W.F., Pan, C.T., Lin, M.C., Wen, Z.H., Liao, C.F., & Shiue, Y.L. (2021). Competitive Real-Time Near Infrared (NIR) Vein Finder Imaging Device to Improve Peripheral Subcutaneous Vein Selection in Venipuncture for Clinical Laboratory Testing. Micromachines, 12(4): 373. https://pubmed.ncbi.nlm.nih.gov/33808493/.

[17] Fraifel, A., & Thompson, J.A. (2023). Incorporating Near Infrared Light Vein Visualization Technology into Peripheral Intravenous Access Protocols. J Infus Nurs., 46(6): 313–319. https://doi.org/10.1097/nan.0000000000000523.

[18] Annalyn, N.S.L., Leow, X.R.G., Ang, W.W., & Lau, Y. (2024). Effectiveness of near-infrared light devices for peripheral intravenous cannulation in children and adolescents: A meta-analysis of randomized controlled trials. J Ped Nurs., 75: e81–e92. https://doi.org/10.1016/j.pedn.2023.12.034.

[19] Roggan, A., Friebel, M., Dorsch, K., Hahn, A., & Muller, G. (1999). Optical properties of circulating human blood in the wavelength range 400–2500 nm. J Biomed Opt., 4(1): 36–46. https://doi.org/10.1117/1.429919.

[20] Krasnodębski, M. (2018). Throwing light on photonics: The genealogy of a technological paradigm. Centaurus, 60: 3–24. https://doi.org/10.1111/1600-0498.12172.

[21] Sarbadhikary, P., George, B.P., & Abrahamse, H. (2022). Paradigm shift in future biophotonics for imaging and therapy: Miniature living lasers to cellular scale optoelectronics. Theranostics, 12(17): 7335–7350. https://doi.org/10.7150/thno.75905.

[22] Zeman, H.D., Lovhoiden, G., & Deshmukh, H. (2000). Optimization of subcutaneous vein contrast enhancement. Proc. SPIE 3911, Biomedical Diagnostic, Guidance, and Surgical-Assist Systems II.

[23] Guillon, P., Makhloufi, M., Baillie, S., Roucoulet, C., Dolimier, E., & Masquelier, A.M. (2015). Prospective evaluation of venous access difficulty and a near-infrared vein visualizer at four French haemophilia treatment centres. Haemophilia, 21: 21–26. https://doi.org/10.1111/hae.12513.

[24] Sánchez-Morago, G.V., Sánchez-Coello, M.D., Villafranca-Casanoves, A., Cantero-Almena, J.M., Migallón-Buitrago, M.E., & Carrero-Caballero, M.C. (2010). Viewing veins with AccuVein AV300. Rev Enferm., 33: 33–38. https://pubmed.ncbi.nlm.nih.gov/20201197/.

[25] Cuper, N.J., Klaessens, J.H., Jaspers, J.E., de Roode, R., Noordmans, H.J., de Graaff, J.C., & Verdaasdonk, R.M. (2013). The use of near-infrared light for safe and effective visualization of subsurface blood vessels to facilitate blood withdrawal in children. Med Eng Phys., 35(4): 433–440. https://doi.org/10.1016/j.medengphy.2012.06.007.

[26] Chiao, F.B., Resta-Flarer, F., Lesser, J., Ng, J., Ganz, A., Pino-Luey, D., Bennett, H., Perkins, C., & Witek, B. (2013). Vein visualization: patient characteristic factors and efficacy of a new infrared vein finder technology. Br J Anaesth., 110(6): 966–971. https://doi.org/10.1093/bja/aet003.

[27] Saito, V.S., Yagi, T., Okazaki, Y., & Jinbo, M. (2013). The use of a near-infrared vascular imaging device for varicose veins. JJPH, 24: 345–349. https://doi.org/10.7134/phlebol.24.345.

[28] Nakasa, T., Ikuta, Y., Tsuyuguchi, Y., Ota, Y., Kanemitsu, M., & Adachi, N. (2019). Application of a peripheral vein illumination device to reduce saphenous structure injury caused by screw insertion during arthroscopic ankle arthrodesis. J Orthop Sci., 24: 697–701. https://doi.org/10.1016/j.jos.2018.12.007.

[29] Chen, G., Cao, Y., Tang, Y., Yang, X., Liu, Y., Huang, D., Zhang, Y., Li, C., & Wang, Q. (2020). Advanced Near-Infrared Light for Monitoring and Modulating the Spatiotemporal Dynamics of Cell Functions in Living Systems. Adv Sci (Weinh), 7(8): 1903783. https://doi.org/10.1002/advs.201903783.

[30] Kowalik, L., & Chen, J.K. (2017). Illuminating developmental biology through photochemistry. Nat Chem Biol., 13(6): 587–598. https://doi.org/10.1038/nchembio.2369.

[31] Li, J., Duan, H., & Pu, K. (2019). Nanotransducers for Near-Infrared Photoregulation in Biomedicine. Adv Mater., 31(33): e1901607. https://doi.org/10.1002/adma.201901607.

[32] Wang, J., Liu, Y., Zheng, S., Wang, X., Zhao, J., Yang, F., Zhang, G., Wang, C., & Chen, P.R. (2019). Time-resolved protein activation by proximal decaging in living systems. Nat., 569(7757): 509–513. https://doi.org/10.1038/s41586-019-1188-1.

[33] Smith, A.M., Mancini, M.C., & Nie, S. (2009). Bioimaging: second window for in vivo imaging. Nat Nanotechnol., 4(11): 710–711. https://doi.org/10.1038/nnano.2009.326.

[34] He, S., Song, J., Qu, J., & Cheng, Z. (2018). Crucial breakthrough of second near-infrared biological window fluorophores: design and synthesis toward multimodal imaging and theranostics. Chem Soc Rev., 47(12): 4258–4278. https://doi.org/10.1039/c8cs00234g.

[35] Hong, G., Antaris, A.L., & Dai, H. (2017). Near-infrared fluorophores for biomedical imaging. Nat Biomed Eng., 1(1): 0010. https://www.nature.com/articles/s41551-016-0010.

[36] Antaris, A.L., Chen, H., Cheng, K., et al. (2016). A small-molecule dye for NIR-II imaging. Nat Mater., 15(2): 235–242. https://doi.org/10.1038/nmat4476.

[37] Greenwald, E.C., Mehta, S., & Zhang, J. (2018). Genetically Encoded Fluorescent Biosensors Illuminate the Spatiotemporal Regulation of Signaling Networks. Chem Rev., 118(24): 11707–11794. https://doi.org/10.1021/acs.chemrev.8b00333.

[38] Yeh, H.W., & Ai, H.W. (2019). Development and Applications of Bioluminescent and Chemiluminescent Reporters and Biosensors. Annu Rev Anal Chem (Palo Alto Calif), 12(1): 129–150. https://doi.org/10.1146/annurev-anchem-061318-115027.

[39] Zhu, S., Tian, R., Antaris, A.L., Chen, X., & Dai, H. (2019). Near-Infrared-II Molecular Dyes for Cancer Imaging and Surgery. Adv Mater., (24): e1900321. https://doi.org/10.1002/adma.201900321.

[40] Yu, N., Huang, L., Zhou, Y., Xue, T., Chen, Z., & Han, G. (2019). Near-Infrared-Light Activatable Nanoparticles for Deep-Tissue-Penetrating Wireless Optogenetics. Adv Healthc Mater., 8(6): e1801132. https://doi.org/10.1002/adhm.201801132.

[41] Mickle, A.D., Won, S.M., Noh, K.N., et al. (2019). A wireless closed-loop system for optogenetic peripheral neuromodulation. Nat., 565(7739): 361–365. https://doi.org/10. 1038/s41586-018-0823-6.

[42] Bettati, S., & Mozzarelli, A. (1997). T state hemoglobin binds oxygen noncooperatively with allosteric effects of protons, inositol hexaphosphate, and chloride. J Biol Chem., 272(51): 32050–32055. https://doi.org/10.1074/jbc.272.51.32050.

[43] Komorowska, M., Cuissot, A., Czarnołęski, A., & Białas, W. (2002). Erythrocyte response to near-infrared radiation. J Photochem Photobiol B: Biol., 68(2–3): 93–100. https://doi.org/10.1016/s1011-1344(02)00361-5.

[44] Chludzińska, L., Ananicz, E., Jarosawska, A., & Komorowska, M. (2005). Near-infrared radiation protects the red cell membrane against oxidation. BCMD, 35(1): 74–77. https://doi.org/10.1016/j.bcmd.2005.04.003.

[45] Ogawa, S., Lee, T.M., Kay, A.R., & Tank, D.W. (1990). Brain magnetic resonance imaging with contrast dependent on blood oxygenation. Proc. Natl. Acad. Sci. U.S.A., 87: 9868–9872. https://doi.org/10.1073/pnas.87.24.9868.

[46] Motta, M., Haik, Y., Gandhari, A., & Chen, C.J. (1998). High magnetic field effects on human deoxygenated hemoglobin light absorption. Bio. Bioenerg., 47(2): 297–300. https://doi.org/10.1016/s0302-4598(98)00165-2.

[47] Bren, K.L., Eisenberg, R., & Gray, H.B. (2015). Discovery of the magnetic behavior of hemoglobin: A beginning of bioinorganic chemistry. Proc. Natl. Acad. Sci. U.S.A., 112 (43): 13123–13127. https://doi.org/10.1073/pnas.1515704112.

[48] Guensch, D.P., Michel, M.C., Huettenmoser, S.P., Jung, B., Gulac, P., Segiser, A., Longnus, S.L., & Fischer, K. (2021). The blood oxygen level dependent (BOLD) effect of in-vitro myoglobin and hemoglobin. Sci Rep., 11(1): 11464. https://doi.org/10.1038/s41598-021-90908-x.

[49] Perutz, M.F. (1970). Stereochemistry of cooperative effects in haemoglobin. Nat., 228(5273): 726–739. https://doi.org/10.1038/228726a0.

[50] Perutz, M.F., Fermi, G., Luisi, B., Shaanan, B., & Liddington, R.C. (1987). Stereochemistry of cooperative mechanisms in haemoglobin. Acc. Chem. Res., 20: 309–321. https://doi.org/10.1021/ar00141a001.